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THE MANIFESTATIONS OF THE PRINCIPLES OF CHEMICAL MECHANICS IN THE LIVING PLANT.¹

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THE UNIFORMITY OF NATURE.

Among the phenomena of nature man finds himself to be one of medium magnitude, for while his dimensions are about a billion times as great as those of the smallest atoms that compose him they are also about one billionth part of his distance from the center of his solar system.

From the vantage point of this medium magnitude the man of science scans eagerly the whole range of natural phenomena accessible to him with a strenuous desire for unity and simplification.

By the unwearying study of special sections of this long front of natural phenomena special guiding principles have been detected at work locally. No sooner has this been accomplished than, in obedience to this desire for continuity throughout, such principles have been freely extended on either side from the point of discovery.

Thus, the theory of probability, which dealt at first with so limited an occupation as drawing white and black balls out of an opaque bag, now is known as the only determinable factor in such remote things as the distribution of the duration of human lives and the effect of concentration of the colliding molecules in a solution upon the rate of their chemical change. Again, the principle of evolution discovered among living things has been

¹ Address of the president of the Botanical Section of the British Association for the Advancement of Science. Dublin, 1908.

extended, till to speak of the evolution of societies, of solar systems, or of chemical elements is now but commonplace.

The biologist, with all his special difficulties, has at least the limitation that he is only concerned with the middle range of the interminable hostile front of natural phenomena, and that for him is ordained the stubborn direct attack, leaving the brilliant attempts at outflanking movements to the astronomers on the one wing and the workers at corpuscular emanations on the other.

The atoms and molecules that the biologist has to deal with do not differ from those passing by the same names in the laboratories of chemistry and physics (at least no one suggests this), and their study may therefore be left to others. At the other end of the scale, with astronomical magnitudes we have not to deal, unless indeed we yield to the popular clamour to take over the canals on Mars as phenomena necessarily of biological causation.

In the study of that particular range of phenomena which is the special allotment of the physiologists, animal and vegetable, we have had ever before us the problem of whether there is not here some discontinuity in nature; whether the play of molecular and atomic forces occurring outside the living organism can ever account for the whole of the complexity and correlation of chemical and physical interactions demonstrable within the living structure.

As yet we are of course far from any answer to this question, and no one in a scientific assembly like this will call upon us for prophecies. Yet the subject to which I shall devote my address has a bearing upon this question. I propose to consider a particular aspect of the relation of chemical changes in a test-tube to those taking place in a living growing plant, and this in the spirit of one who craves for continuity throughout natural phenomena.

The point of view from which the chemist regards the reaction taking place in his test-tube has undergone a

change in the last twenty years, a change bringing it more into uniformity with that of the biologist. No longer content with an equation as a final and full expression of a given reaction, the chemist now studies with minutest detail and with quantitative accuracy the progressive stages of development of the reaction² and the effect upon it of varied external conditions, of light, temperature, dilution, and the presence of traces of foreign substances.

Perhaps it is too much to believe that this, as it were physiological, study of each reaction is the effect of some benign irradiation from the biological laboratory. At least, however, it is true that it is the modern study of "slow" chemical reactions which has made all this possible, and the living organism consists almost entirely of slow reactions. The earliest studied chemical reactions, those between substances which interact so quickly that no intermediate investigation can be made, did not of course lend themselves to this work, but nowadays whole classes of reactions are known which are only completed hours or days after the substances are initially mixed. To the slow reactions belong all the hydrolytic and dehydration changes of carbohydrates, fats and proteids that bulk so largely in the metabolism of plants and animals, together with other fermentation changes such as are brought about by oxidases, zymases and enzymes in general. This precise quantitative study of chemical reactions has been developing with remarkable acceleration for some twenty-five years, till it is grown almost into an independent branch of science, physical chemistry. This is sometimes called "general chemistry" because its subject is really the fundamental universal laws of the rate of chemical change, and these laws hold through all the families, genera and species of chemical compounds, just as the same physiological laws apply to all the different types of plants.

² Modern research has made it clear that reactions conventionally represented by complex equations of many interacting molecules really take place in a succession of simple stages, in each of which, perhaps, only two molecules interact.

Now if these laws are fundamental with all kinds of chemical change they must be at work in the living metabolic changes. If the chemical changes associated with *protoplasm* have any important factor or condition *quite different* from the state of things which holds when molecules react in aqueous solution in a test-tube, then it might happen that the operation of these principles of physical chemistry would be obscured and not very significant, though it is inconceivable that they should be really inoperative.

My present intention, then, is to examine the general phenomena of metabolism in an attempt to see whether the operations of these quantitative principles are traceable, and if so how far they are instrumental in giving a clearer insight into vital complexity.

THE DOMINANCE OF IRRITABILITY IN PHYSIOLOGY.

I think that certain manifestations of these principles are indeed quite clear, though not generally recognized, and that this neglect is largely due to the dominance of what our German colleagues call "*Reizphysiologie*"—the notion that *every* change in which protoplasm takes part is a case of the "*reaction*" of an "*irritable*" living substance to a "*stimulus*." Now this general conception of protoplasmic irritability, of stimuli and reactions was, of course, a splendid advance, the early development and extension of which we owe largely to our veteran physiologist Professor Pfeffer, of Leipzig. Great as is the service it has rendered to many departments of botany, yet in one direction, I think, it has overflowed its legitimate bounds and swamped the development of the physical-chemical concepts which I shall indicate later on. The great merit of the "*stimulus and reaction*" conception is that it supplies a very elastic general formula for the sort of causal connection that we find occurring in all departments of biology; a formula which allows the phenomena to be grouped, investigated and formally expounded, whether they be the temporary turgor-movements of "*sensitive*"

plants, the permanent growth movements of tropistic curvatures, or the complex changes of plant-form and development that result from present and past variations of external conditions.

The strength and the weakness of the conception lie in its extraordinary *lack of particularity*. When an irritable cell responds to a stimulus by a reaction nothing is implied about the mechanism connecting the *cause and the effect*, and nothing even about the relative magnitudes of these, but all this is left for special research on the case under consideration. The one natural chain of cause and effect that is recognized to be outside this comprehensive category is that rather uncommon one in which a definite amount of energy of one kind is turned into an equivalent definite amount of energy of another. Here we have a direct "equation of energy," whereas in a reaction to a stimulus we are said to have typically an "unloosing" effect—a liberation of potential energy by a small incidence of outside energy, as in the classical analogies, drawn from completely comprehended non-living things, of a cartridge exploded by a blow, or the liberation into action of a head of water by the turning of a tap.

So elastic a conception may be easily stretched to fit almost any sequence of phenomena with the apparent closeness that argues a bespoke garment. We must therefore be critically on our guard against cases of such sartorial illusion.

THE PRINCIPLES OF CHEMICAL MECHANICS.

That my consideration of particular cases may be intelligible it seems necessary that I devote a few minutes to outlining the four quantitative mechanical principles which govern every single chemical reaction, though much that I have to say has been drawn from elementary books on physical chemistry.

These four principles are concerned with (1) the nature of the reaction in question; (2) the amount of reacting substances that happen to be present; (3) the temperature

at which the reaction is taking place; and (4) the influence of catalysts upon the reaction.

For the moment we will confine ourselves to the first two matters, and assume that catalysts are absent and the substances at constant temperature.

1. The first principle that we have to consider is that which declares that no chemical reaction is really instantaneous, though the interaction of substances is often so fast that a direct measurement of its rate can not be made; and, further, that every reaction has its own *specific reaction-velocity* which distinguishes it from other reactions. This is expressed by giving to each particular reaction a numerical *velocity coefficient* which is low or high proportionally as the reaction is slow or quick.

2. This coefficient only expresses the actual experimental velocity when the reacting substances are present in *unit* concentration, because difference of concentration is just the most important factor controlling the actual reaction-velocity.

If a solution of a substance *A* of unit concentration is undergoing change, then to keep this reaction going at its present rate fresh amounts of *A* must be added continually just to equal the amount removed by the reaction and so keep the substance up to unit concentration. The amount of *A* that had to be added thus per unit time would give an exact measure of the amount being decomposed, *i. e.*, of the specific velocity of this reaction.

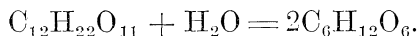
If the reaction were started with *A* at double unit concentration, then twice as much *A* would have to be added *per* unit time to keep the reaction velocity constant at the double rate it would have started at.

And with higher concentrations proportionally more *A* would have to be added. It is therefore shown that the amount of chemical change going on in unit time is proportional to the concentration. This is a most fundamental principle of chemical mechanics, known as the *law of mass*, and it may be stated thus: *the amount of chemical change taking place at any time is always propor-*

tional to the amount of actively reacting substance (or substances) present.

To carry out experiments by the procedure given above is in practise very difficult and the velocities of reactions are never measured by the chemist in this way. In a living organism this continual bringing up of new supplies of material to maintain a constant rate of change is the ordinary way of life, but in the chemical laboratory procedure is different. There, definite amounts of substances are initially mixed in a vessel and the reaction is allowed to progress by itself without further additions. In this case there is a continual falling off of the concentration of the substance, and so a corresponding diminution of the actual reaction-velocity.

In this procedure the diminution of the initial amount of substance can be actually measured by withdrawing small samples at intervals of time and analyzing them. Let us consider a definite example. Cane-sugar can be hydrolyzed, under various conditions, to give two molecules of hexose, according to the equation



This reaction goes on, though extremely slowly, when an aqueous solution of cane-sugar is kept very hot in a beaker. Suppose we started with, say 128 grams dissolved in a liter of water and traced the diminution of this amount down towards zero by withdrawing samples at intervals of time and analyzing them. If we plotted the sugar-content of these successive samples against the times when they were taken we should get the curve given in Fig. 1. If we call n minutes the time taken for the sugar to diminish from 128 grams to 64 grams, we should find that in the second n minutes the sugar had fallen to 32 grams, after $3n$ minutes to 16 grams, and so on, the amount halving itself every n minutes. Thus the amounts of cane-sugar hydrolyzed in successive equal intervals are 64, 32, 16, 8, 4, 2, 1 grams, amounts in each case just exactly proportional to the quantity of

cane-sugar then remaining in solution, thus exemplifying the law of mass.

Such a curve as *A* in Fig. 1, which changes by a constant multiple for successive units of time (here halving itself every *n* minutes) is known as a logarithmic curve; the velocity of reaction at any moment is exactly indicated by the steepness of the curve at that moment; the velocity is greatest at first and it declines to almost zero as the curve approaches the horizontal at the end of the reaction.

When instead of the decomposition of a single substance we deal with two dissolved substances, *A* and *B*, reacting together, then as *both* of them go on being thus used up, the amount of change must be ever proportional to the mass or amount of *A* present multiplied by the mass of *B* present.

There is a special important case when the amount of, say, *B* is in very great excess of that amount required to unite with the whole of *A*. Then all through the slow progress of the reaction the amount of *B* never becomes reduced enough to make appreciable difference to its mass, and it may be considered as practically constant all along. In such a case the rate of the reaction is found to be proportional simply to the amount of *A* present, and we get again the curve *A*, Fig. 1. Here the amount of *A* may be considered as a limiting factor to the amount of reaction; *B* being in such great excess never falls low enough to take a practical part in determining the velocity.

The case of the hydrolysis of cane-sugar in aqueous solution is just such a case. The water itself enters into the reaction, but so little is used up in relation to the enormous excess present that the amount remains practically constant and the rate of hydrolysis of the cane-sugar is determined only by the amount of the cane-sugar present at any moment.³

3. We have now shown how the actual amount of chemical change going on in a solution is determined by the

³ 128 grams cane-sugar unite with 6.7 grams water in hydrolysis, and in our experiment nearly 1,000 grams of water are present.

combined effect of (1) the specific reaction velocity and (2) the law of mass. We have next to point out that the specific reaction coefficient is not the same under all circumstances, but is affected by variations of external conditions, always by temperature, and generally by the presence of traces of so-called catalysts.

The relation to temperature we will postpone, and proceed to consider our third principle, the acceleration of reaction velocity by *catalytic agents*.

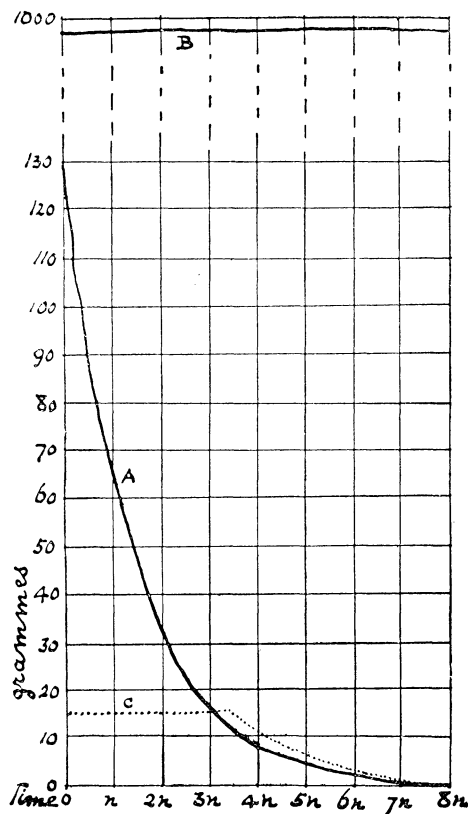


FIG. 1.

It has long been known that small additions of various foreign substances may have a great effect in increasing the rate at which a reaction is proceeding. Thus this hydrolysis of cane-sugar, so slow with pure water, goes at a

fair velocity if a few drops of a mineral acid are added to the solution, while the addition of a trace of a particular enzyme (invertase from plant or animal) enormously increases the rate of change, so that the whole 128 grams of cane-sugar are soon hydrolyzed to hexose. The reaction progresses quantitatively in the same sort of way as before, giving a logarithmic curve of sugar-content. Indeed the same graphic curve, Fig. 1, *A*, would represent the facts if the value of *n* were reduced from many hundred minutes to quite a few.

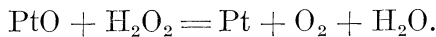
The most striking point about this new state of things is that the added body is not used by its action, but the acid or enzyme is still present in undiminished amount when the reaction is completed.

Such actions were at first styled "contact" actions, but are now known as catalytic actions, because we have learned that the catalyst does not work just by contact but by combining with the sugar to form an intermediate addition compound, and that this compound is then split up by the water liberating the catalyst again, but freeing the sugar part, not as cane-sugar, but combined with the water to form two molecules of hexose.

On many chemical reactions, finely divided metals such as platinum and gold have a very powerful catalytic action. Thus platinum will cause gaseous hydrogen and oxygen to unite at ordinary temperatures, and will split up hydrogen dioxide with the formation of oxygen. The intermediate stages in this catalytic decomposition may be summarily simplified to this—



and



Thus the reaction goes on and on by the aid of the appearing and disappearing "intermediate compound" PtO till at the end the H_2O_2 is all decomposed and the platinum is still present unaffected.

The enzymes are the most powerful catalytic agents

known, and most of them are specifically constituted to effect the hydrolysis, oxidation, reduction or splitting of some definite organic compound or group of compounds containing similar radicals.

Innumerable enzymes have in late years been isolated from the plant-body, so that it would seem that there is none present to catalytically accelerate each of the slow single changes that in the aggregate make up the complex metabolism of the plant.

The law of mass applies with equal cogency to *catalytic* reactions. If twice the amount of acid is added to a solution of cane-sugar (or twice the amount of enzyme) then the reaction velocity is doubled, and hydrolysis proceeds twice as fast. As the catalyst is not destroyed by its action, but is continually being set free again, the concentration of the catalyst remains the same throughout the reaction; while, on the contrary, the amount of cane sugar continually decreases.

If the catalyst be present in great excess the amount of hydrolysis will be limited by the amount of cane-sugar present, and as this is used up so the reaction will progress by a logarithmic curve as in Fig. 1, *A*. In this case *B* may represent the amount of catalyst. If, on the contrary, there is a large amount of sugar and very little acid or enzyme present, so that the catalyst becomes the limiting factor, then we happen upon a novel state of things; for by the law of mass the rate of hydrolysis will now remain constant for some time till the excess of sugar is so far reduced that it in turn becomes a limiting factor to the rate of change. In this case the velocity curve would consist of a first phase with a straight horizontal line of uniform reaction-velocity leading into the second phase of a typical falling logarithmic curve (see Fig. 1, *C*). These conditions have been experimentally examined by Horace Brown and Glendinning, and fully explained and expounded by E. F. Armstrong in Part II of the critical "Studies in Enzyme Action."⁴

⁴ *Proc. Roy. Soc., Vol. LXXIII, 1904, p. 511.*

Having now outlined the three fundamental principles of reaction-velocity, the law of mass, and the catalytic acceleration of reaction-velocity, we are in a position to consider the broad phenomena of metabolism or chemical change in the living organism from the point of view of these principles of chemical mechanics.

THE METABOLISM OF THE PLANT CONSIDERED AS A CATALYTIC REACTION.

Plants of all grades of morphological complexity, from bacteria to dicotyledons, have this in common, that throughout their active life they are continually growing. Putting aside the *qualitative* distribution of growth that determines the morphological form, as a stratum of phenomena above the fundamental one that we are about to discuss, we find that this growth consists in the assimilation of dead food-constituents by the protoplasm with a resulting increase in the living protoplasm accompanied with the continual new formation of dead constituents, gaseous CO₂, liquid water, solid cellulose, and what not. This continual flux of anabolism and katabolism is the essential character of metabolism, but withal the protoplasm increases in amount by the excess of anabolism over katabolism.

Protoplasm has essentially the same chemical composition everywhere, and in the whole range of green plants the same food-materials seem to be required; the six elements of which proteids are built are obviously essential in quantity as building material, but in addition small amounts of Fe, Ca, K, Mg, Na, Cl and Si are in some other way equally essential. What part these secondary elements play is still largely a matter of hypothesis.

Regarding metabolism thus crudely as if it were merely a congeries of slow chemical reactions, let us see how far it conforms to the laws of chemical mechanics we have outlined.

If the supply of any one of these essential elements comes to an end, growth simply ceases and the plant

remains stationary, half-developed. If a *Tropæolum* in a pot be watered with dilute salt-solution, its stomata soon close permanently, and no CO_2 can diffuse in to supply the carbon for further growth of the plant. In such a condition the plant may remain for weeks looking quite healthy, but its growth may be quite in abeyance.

In agricultural experience, in manuring the soil with nitrogen and the essential secondary elements, the same phenomenon is observed when there is a shortage of any single element. If a continuous though inadequate supply of some one element is available then the crop development is limited to the amount of growth corresponding to this supply. Agriculturalists have formulated the "law of the minimum," which states that the crop developed is limited by the element which is minimal, *i. e.*, most in deficit. Development arrested by "nitrogen-hunger" is perhaps the commonest form of this. All this is of course in accordance with expectation on physical-chemical principles. The quantity of anabolic reaction taking place should be proportional to the amount of actively reacting substances present, and if any one essential substance is quite absent the whole reaction must cease. It therefore seems clouding a simple issue and misleading to say of a plant which, from the arrested development of nitrogen-hunger, starts growth again when newly supplied with nitrogen, that this new growth is a response to a "*nitrogen stimulus*." It would appear rather to be only the removal of a limiting condition.

Let us now move on a stage. Suppose a growing plant be liberally supplied with all the thirteen elements that it requires, what, then, will limit its rate of growth? Fairy bean-stalks that grow to the heavens in a night elude the modern investigator, though some hope soon to bring back that golden age with overhead electric wires and underground bacterial inoculations. If everything is supplied, the metabolism should now go on at its highest level, and quantities of carbon, nitrogen, hydrogen and oxygen supplied as CO_2 , nitrates and water will interact so that these

elements become converted into proteid, cellulose, etc. Now this complex reaction of metabolism only takes place in the presence of protoplasm, and a small amount of protoplasm is capable of carrying out a considerable amount of metabolic change, remaining itself undestroyed. We are thus led to formulate the idea that metabolism is essentially a catalytic process. In support of this we know that many of the inherent parts of the protoplasmic complex are catalytic enzymes, for these can be separated out of the protoplasm, often simply by high mechanical pressure. We know, too, nowadays that the same enzymes that accelerate katabolic processes also accelerate the reverse anabolic processes.

In time a small mass of protoplasm will, while remaining itself unchanged, convert many times its own weight of carbon from, let us say, the formaldehyde (HCHO) of photosynthesis to the carbon dioxide (CO_2) of respiration.

If metabolism is a complex of upgrade and downgrade changes catalyzed by protoplasm we must expect the amount of metabolism to obey the law of mass and to be proportional to the masses of substances entering into the reaction. The case when any one essential element is a limiting factor we have already considered. When all are in excess, then the *amount of the catalyst present* becomes in its turn the limiting factor. Transferring this point of view to the growing plant, we expect to find the limited mass of protoplasm and its constituent catalysts setting a limit to the rate of metabolic change in the extreme case where all the materials entering into the reaction are in excess. When once this supply is available further increase in supplies can not be expected to accelerate the rate of growth and metabolism beyond the limit set by the mass of protoplasm. This, of course, is in accordance with common experience. The clearest experimental evidence is in connection with respiration and the supply of carbohydrates—this, no doubt, because the carbohydrate material oxidized in respiration is normally stored inside plant-cells in quantity and can be estimated. When the

supplies for an internal process have to be obtained from outside, then we have the complications of absorption and translocation to obscure the issue, especially in the case of a higher plant.

Let us first take a case where the carbohydrate supply is in excess and the amount of catalytic protoplasm is small and increasing. Thus it is in seeds germinating in the dark: respiration increases day by day for a time, though carbohydrate reserves are steadily decreasing. Palladine⁵ has investigated germinating wheat by analyzing the seedlings and determining the increase of the essential (non-digestible) proteids day by day. The amount of these proteids he regards as a measure of the amount of actual protoplasm present. Assuming this to be so, he finds an approximately constant ratio between the amount of protoplasm at any stage and the respiration.

As germination progresses in the dark the supplies of reserve carbohydrate presently fail, and then the respiration no longer increases in spite of the abundant protoplasm. According to our thesis the catalyst is now in excess and the CO_2 production is limited by the shortage of respirable material.

This second type of case was more completely investigated by Miss Matthæi and myself in working on the respiration of cut leaves of cherry-laurel kept starved in the dark. For a time the CO_2 production of these non-growing structures remains uniform, and then it begins to fall off in a logarithmic curve, so that the course of respiration is just like *C* in Fig. 1. We interpret both phenomena in the same way: in the initial level phase the respirable material in the leaf is in excess, and the amount of catalytic protoplasm limits the respiration to the normal biological level; in the second falling phase some supply of material is being exhausted, and we get a logarithmic curve controlled by the law of mass, as much, it would seem, as when cane-sugar is hydrolyzed in aqueous solution.

After these two illustrations of the action of the law

⁵ *Revue gén. de botanique*, Tome VIII, 1896.

of mass from the more simple case of respiration we return to the consideration of the totality of metabolic reactions as exemplified in growth.

What should we expect to be the ideal course of growth, that is, the increase of the mass of the plant regarded as a complex of reactions catalyzed by protoplasm? Let us consider, first, the simplest possible case, that of a bacterium growing normally in a rich culture solution. When its mass has increased by anabolism of the food material of the culture medium to a certain amount it divides into two. As all the individuals are alike, counting them would take the place of weighing their mass. The simplest expectation would be that, under uniform conditions, growth and division would succeed each other with monotonous regularity, and so the number or mass of bacteria present would double itself every n minutes. This may be accepted as the ideal condition.

The following actual experiment may be quoted to show that for a time the ideal rate of growth is maintained, and that at the end of every n minutes there is a doubled amount of protoplasm capable of catalyzing a doubled amount of chemical change and carrying on a doubled growth and development.

From a culture of *Bacillus typhosus* in broth at 37° C. five small samples were withdrawn at intervals of an hour, and the number of bacteria per unit volume determined by the usual procedure. The number of organisms per drop increased in the following series: 6.7, 14.4, 33.1, 70.1, 161.0.⁶ This shows a doubling of the mass of bacteria in every fifty-four minutes and is the case actually represented in the strictly logarithmic curve of Fig. 2.

We may quote some observations made by E. Buchner⁷ of the rate at which bacteria increase in culture media. *Bacillus coli communis* was grown at 37° C. for two to

⁷ Buchner. Zuwachsgrossen u. Wachstumsgeschwindigkeiten. Leipzig, 1901.

⁶ For this unpublished experiment on bacterial growth I am indebted to Miss Lane-Clayton of the Lister Institute of Preventive Medicine.

five hours, and by comparison of the initial and final numbers of bacteria the time required for doubling the mass was calculated. Out of twenty-seven similar experiments a few were erratic, but in twenty cases the time for doubling was between 19.4 and 24.8 minutes, giving a mean of 22 minutes. This produces an increase from 170 to 288,000 in four hours. No possible culture medium will provide for prolonged multiplication of bacteria at these rates.

Cohn^s states that if division takes place every sixteen minutes then in twenty-four hours a single bacterium $1\ \mu$ long will be represented by a multitude so large that it requires twenty-eight figures to express it, and placed end to end they would stretch so far that a ray of light to travel from one end to the other would take 100,000 years. The potentialities of protoplasmic catalysis are thus made clear, but the actualities are speedily cut short by limiting factors.

For a while, however, this ideal rate of growth is maintained. At the end of every n minutes there is a doubled amount of protoplasm present, and this will be capable of catalyzing twice the amount of chemical change and carrying on a doubled amount of growth and development. This is what common sense and the law of mass alike indicate, and is exactly what this logarithmic curve in Fig. 2 expresses.

This increase of the amount of catalytic protoplasm by its own catalytic activity is an interesting phenomenon. In Section K we call it growth, attribute it to a spe-

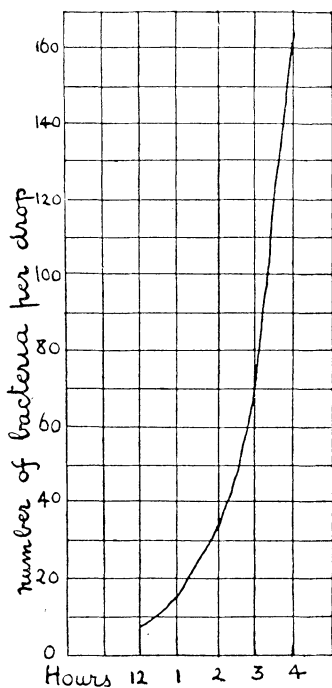


FIG. 2.

^s Cohn. *Die Pflanze*. Breslau, 1882, p. 438.

cific power of protoplasm for assimilation (in the strict sense), and leave it alone as a fundamental phenomenon, but are much concerned as to the distribution of the new growth in innumerable specifically distinct forms. In the Chemical Section they call this class of phenomenon "autocatalysis," and a number of cases of it are known. In these a chemical reaction gives rise to some substance which happens to catalyze the particular reaction itself, so that it goes on and on with ever-increasing velocity. Thus, we said that free acid was a catalyst to the hydrolysis of cane-sugar; suppose now that free acid were one of the products of the hydrolysis of sugar, then the catalyst would continually increase in amount in the test-tube, and the reaction would go faster and faster. Under certain conditions this actually happens. Again, when methyl acetate is hydrolyzed we normally get methyl alcohol and free acetic acid. This free acid acts as a catalyst to the hydrolysis, and the rate of change continually accelerates. Here, if the supply of methyl acetate were kept up by constant additions, the reaction would go faster and faster with a logarithmic acceleration giving a curve of velocity identical with Fig. 2, *A*.

For a clear manifestation of this autocatalytic increase in the plant it is, of course, essential that the supply of food materials to the protoplasm be adequate.

Another case where we might look for a simple form of this autocatalytic increase in the rate of conversion of food materials to anabolites would be in the growth of a filamentous alga, like *Spirogyra*. Here, as in the bacterium, all the cells are still capable of growth. In this case the food-material needed in greatest bulk is carbon, which has to be obtained by photosynthesis. Some experiments have been started in the Cambridge Laboratory on the rate of growth of *Spirogyra* in large tubs of water kept at different temperatures and with varying facilities for photosynthesis and metabolism. Under rather depressing conditions the *Spirogyra* took several days to double its weight—a rate of metabolism out of all comparison slower than that of bacteria. Experiments on these

lines, with the different food materials as limiting factors, should give instructive results.

We turn now to consider the growth of a flowering plant. Here conditions are more complex, and we know that at the flowering stage or end of the season the growth diminishes considerably. This difference from a simple alga or bacterium we can only regard as a secondary acquisition in relation to the external conditions—either a reaction to a present external stimulus or to the memory of past stimuli. In a flowering plant, too, all the cells do not continue to grow; many cells differentiate and cease to grow and also some of the groups of meristem remain dormant in axillary buds. Clearly the growth curve can not continue to accelerate logarithmically, and in later phases it must tail off; the “grand period” which growth is said to exhibit is another way of stating this. It will, however, be of great interest to us to see what will be the form of the curve of growth during the early period of development.

The importance of this class of work has been realized in Geneva, and detailed work is now being done under the inspiration of Professor Chodat⁹ in which the curve not only of growth (fresh weight) but of the uptake of all the separate important elements in selected plants is being carefully followed.

With plants grown in the open, climatic disturbances must occur. We shall therefore figure a curve for the fresh weight of a maize plant grown in water-culture. This is prior to the Geneva work, and due to Mlle. Stefanowska,¹⁰ who has studied also the growth-curves of small animals. The first phase of the curve, lasting some fifty days, shows strictly uniform acceleration, doubling

⁹ Monnier, A. *Les matières minérales et la loi d'accroissement des végétaux*. Geneva, 1905.

Déléano, N. *Le rôle et la fonction des sels minéraux dans la vie de la plante*. Geneva, 1907.

See also the independent work of Tribot. *Comptes rendus de l'Acad. des Sciences*, October 14, 1907.

¹⁰ Stefanowska. *Comptes rendus de l'Acad. des Sciences*, February 1, 1904.

the weight of the plant every ten days (Fig. 3). The precise external conditions are not stated.

In spite of the morphological complexity the autocatalytic reaction of growth is apparently not checked by inadequate supplies before the plant enters rather suddenly upon the second phase. Here, from the present point of view, we consider that the progress of growth is interrupted, not by the primary physical-chemical causes, but by secondary causes, presumably to be classed in the category of stimulus and reaction.

The numerous curves for the accumulation of different organic and mineral constituents worked out for barley

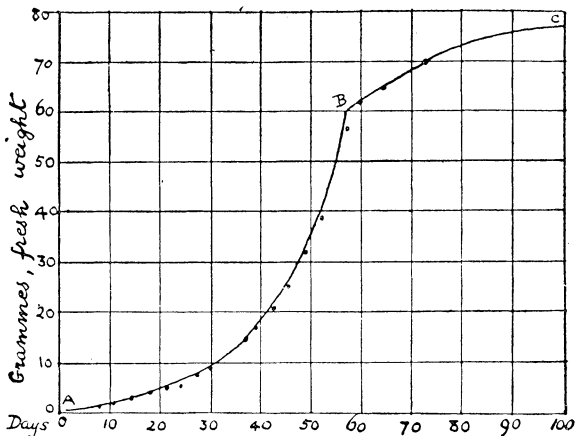


FIG. 3.

and buckwheat at Geneva are of similar form, but do not keep up the uniform rate of doubling so well as does the curve of total fresh weight.

In this connection the tall and dwarf forms of the same plant present an interesting problem, and some experiments have been started on sweet peas at Cambridge. At the time of germination the seedlings weigh about the same, whereas at the end of the season the weight of a tall plant is many times that of a dwarf "cupid" growing alongside under similar conditions. Is the difference due to a less vigorous autocatalysis in the dwarf form, so that throughout its growth it takes a greater number

of days to double its weight? Construction of the curves of growth through the season will show whether it is this or some other alteration in the form of the curve.

I now propose to say a few words about one last point in connection with growth considered as a phenomenon of catalysis before passing on to deal with the effects of temperature.

Of the metallic elements that are essential for the growth of plants some occur in such minute quantities that one can only imagine their function is catalytic. If iron, for instance, played any part in metabolism which involved its being used up in any building material or by-product of metabolism, then a larger amount than actually suffices should be advantageous. If its function is catalytic the iron would go on acting indefinitely without being consumed, and so a minute trace might serve to carry out some essential, and even considerable, sub-section of metabolism.

Elements like manganese, magnesium and iron are often associated with non-vital catalytic action, and a preparation of iron has recently been quantitatively investigated which seems to have literally all the properties of an organic oxydase from plant tissues.¹¹

As long ago as 1869 Raulin observed that traces of unessential salts, in particular those of zinc, added to the culture medium in which he grew the fungus *Sterigmatozystis* caused a rapid acceleration of the growth rate. The time that the mycelium took to double its weight was now reduced to a half or even a third. This continued enormous effect of so small a trace of substance is possibly to be regarded as an added catalyst to the normal protoplasmic apparatus. This sort of effect is currently labeled "chemical stimulation" and has been interpreted as an attempt of the fungus to grow away from an unpleasant environment. To me it looks as if such chemical stimulation were really another example of the in-

¹¹ Wolff, J. Des péroxydiastases artificielles. *Comptes rendus de l'Acad. des Sciences*, June 9, 1908.

judicious extension of the concept of stimulus and reaction.

This effect of zinc upon the growth of mycelium has recently been verified and extended by Javillier,¹² who has made comparative cultures with increasing doses of zinc salt. He grew *Sterigmatocystis* for four days at 34° C. in media with graded additions of zinc salts. As the graphic representation shows, he finds a continuous

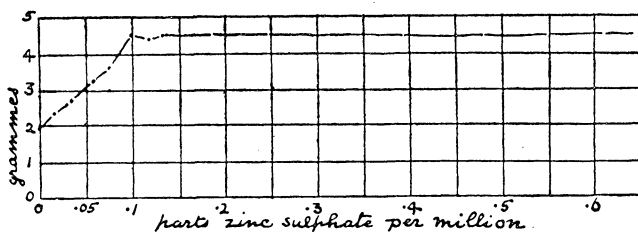


FIG. 4.

regular increase of the number of grams of final dry weight with doses up to 0.00001 per cent., and then no greater but an equal effect up to 100 times as large a dose.

This form of curve with uniform rise at first, abruptly changing to a level top, suggests, as I have pointed out elsewhere,¹³ the cutting-off of the primary rising effect by a limiting factor. In this case presumably the limit set by some other sub-section of the metabolism has been attained.

ACCELERATION OF REACTION-VELOCITY BY TEMPERATURE.

We now turn to consider the fourth and last of the principles of chemical mechanics which we might expect to find manifested in metabolism.

It is a universal rule that rise of temperature quickens the rate at which a chemical reaction proceeds. Of course in some rare conditions this may not be obvious, but be obscured by superposed secondary causes; but almost always this effect is very clearly marked.

Further, the nature of the acceleration is a peculiar

¹² *Comptes rendus de l'Acad. des Sciences*, December, 1907.

¹³ Optima and Limiting Factors. *Annals of Botany*, Vol. XIX, April, 1905.

one. Rise of temperature affects nearly all physical and chemical properties, but none of these is so greatly affected by temperature as is the velocity of chemical reaction. For a rise of 10° C. the rate of a reaction is generally increased two or three fold, and this has been generalized into a rule by van't Hoff. As this increase is repeated for each successive rise of 10° C. either by the same factor or a somewhat smaller one, the acceleration of reaction-velocity by temperature is logarithmic in nature, and the curve representing it rises ever more and more steeply. Thus keeping within the vital range of temperature a reaction with a temperature factor of $\times 2$ per 10° C. will go sixteen times as fast at 40° C., as at 0° C., while one with a factor of $\times 3$ will go eighty-one times as fast.

This general law of the acceleration of reactions by temperature holds equally for reactions which are being accelerated by the presence of catalysts. As we regard the catalyst as merely providing for the particular reaction it catalyzes, a quick way round to the final stage by passing through the intermediate stage of forming a temporary addition-compound with the catalyst itself, so we should expect rise of temperature to accelerate similarly these substituted chemical reactions.

If this acceleration is a fundamental principle of chemical mechanics it is quite impossible to see how vital chemistry can fail to exhibit it also.

ACCELERATION OF VITAL PROCESSES BY TEMPERATURE.

At present we have but a small number of available data among plants to consider critically from this point of view. But all the serious data with which I am acquainted, which deal with vital processes that are to be considered as part of the protoplasmic catalytic congeries, do exhibit this acceleration of reaction-velocity by temperature as a primary effect.¹⁴

¹⁴ A collection of twenty cases, mostly from animal physiology, by Kanitz (*Zeits. für Elektrochemie*, 1907, p. 707), exhibits coefficients ranging from 1.7 to 3.3.

Let us briefly consider these data. On the katabolic side of metabolism we have the respiratory production of CO_2 , and opposed to it on the anabolic side the intake of carbon in assimilation.

As a measure of the rate of the metabolic processes constituting growth we have data upon the division of flagellates; and finally there is the obscure process of circulation of protoplasm.

The intensity of CO_2 production is often held to be a measure of the general intensity of metabolism, but any relation between growth-rate and respiration has yet to be clearly established. Our science is not yet in the stage when quantitative work in relation to conditions is at all abundant; we are but just emerging from the stage that chemistry was in before the dawn of physical chemistry.

Taken by itself the CO_2 -production of an ordinary green plant shows a very close relation with temperature. In the case of the cherry-laurel worked out by Miss Matthæi and myself the respiration of cut leaves rises by a factor of 2.1 for every 10°C . (See Fig. 5, Resp.) This has been investigated over the range of temperatures from 16°C . to 45°C . At this higher temperature the leaves can only survive ten hours in the dark, and their respiration is affected in quite a short time, but in the initial phases the CO_2 output has the value of .0210 gr. per hour and unit weight of leaf, while at 16.2°C . the amount is only .0025 gr. CO_2 . Thus the respiration increases over a range of tenfold with perfect regularity solely by increase of temperature. No reaction in a test-tube could show less autonomy. At temperatures above 45°C . the temperature still sooner proves fatal unless the leaf is illuminated so as to carry out a certain amount of photosynthesis and compensate for the loss of carbon in respiration. Thus, with rising temperature, there is at no time any sign of an optimum or of a decrease of the intensity of the *initial* stage of respiration.

Here, then, on the katabolic side of metabolism we have no grounds for assuming that "temperature-stimuli" are at work regulating the intensity of protoplasmic respira-

tion, but we find what I can only regard as a purely physical-chemical effect. The numbers obtained by Clausen¹⁵ for the respiration of seedlings and buds at different temperatures indicate a temperature coefficient of about 2.5 for a rise of 10° C.

To this final process of katabolism there could be no greater contrast than the first step of anabolism, the assimilation of carbon by the protoplasm as a result of photosynthesis. We must therefore next inquire what is the relation of this process to temperature.

This question is not so simple, as leaves can not satisfactorily maintain the high rate of assimilation that high temperatures allow. The facts of the case were clearly worked out by Miss Matthæi,¹⁶ the rate of assimilation by cherry-laurel leaves being measured from -6° C. to + 42° C. Up to 37° C. the curve rose at first gently and then more and more steeply, but on calculating out the values it is found that the acceleration for successive rises of 10° C. becomes less and less. Between 9° C. and 19° C. the increase is 2.1 times, the highest coefficient measured, and exactly the same coefficient as for respiration in this plant, which in itself is a striking point, seeing how different the processes are. (See Fig. 5, Assimilation.)

The decrease of the coefficient with successive rises is a state of things which is quite general among non-vital reactions. A critical consideration of the matter leads one to the conclusion, however, that this failure to keep up the temperature acceleration is really due to secondary causes, as is also the appearance of an optimum at about 38° C. Some of these causes, have been discussed by me elsewhere,¹⁷ and I hope to bring a new aspect of the matter before the section in a separate communication. The conclusion formerly come to was that probably in its initial stages assimilation at these very high tempera-

¹⁵ *Landwirtschaftliche Jahrbücher*, Bd. XIX, 1890.

¹⁶ *Phil. Trans. Roy. Soc.*, Ser. B, Vol. CXC VII, 1904.

¹⁷ Optima and Limiting Factors. *Annals of Botany*, Vol. XIX, April, 1905.

tures started at the full value indicated by a theoretically constant coefficient, but that the protoplasm was unable to keep up the velocity, and the rate declined. It must be borne in mind here that quite probably no chloroplast

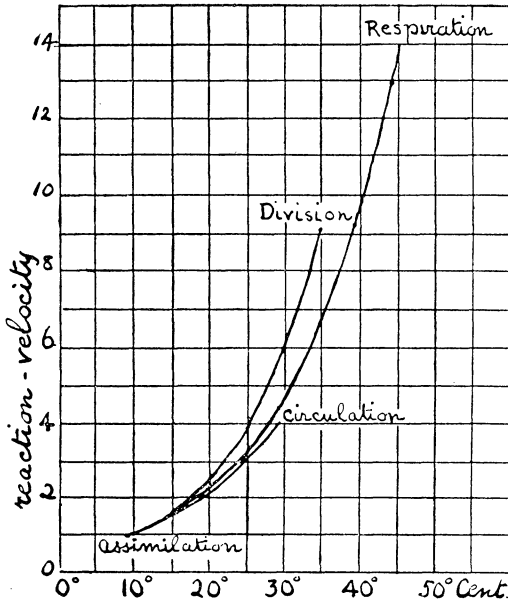


FIG. 5.

since the first appearance of green cells upon the earth had ever been called upon for anything like such a gastronomic effort as these cherry-laurel leaves in question. It is not to be wondered that their capacities speedily declined at such a banquet, and that the velocity-reaction of anabolic synthesis traces a falling curve in spite of the keeping up of all the factors concerned, to wit, temperature, illumination, and supply of CO_2 . This decline is not permanent, but after a period of darkening the power of assimilation returns. Physical-chemical parallels can easily be found among cases where the accumulation of the products of a reaction delays the apparent velocity of the reaction, but this complicated case may be left for further research.

In relation to assimilation, then, we must say that

owing to secondary causes the case is not so clear over the whole range of temperature as that of respiration, but that at medium temperatures we have exactly the same relation between reaction-velocity and temperature.

We may consider now some data upon the combined net result of anabolic and katabolic processes. Such total effects are seen in their clearest form among unicellular saprophytic organisms for which we have a few data. Mlle. Maltaux and Professor Massart¹⁸ have published a very interesting study of the rate of division of the colorless flagellate *Chilomonas paramecium* and of the agents which they say stimulate its cell-division, in particular alcohol and heat.

They observed under the microscope the time that the actual process of division into two took at different temperatures. From 29 minutes at 15° C. the time diminished to 12 minutes at 25° C., and further to 5 minutes at 35° C. The velocities of the procedure at the three temperatures 10° C. apart will therefore be in the ratio of 1 : 2.4 : 5.76, which gives a factor of 2.4 for each rise of 10° C. (See Fig. 5, Division.)

Now we are told by the investigators that at 35° C. *Chilomonas* is on the point of succumbing to the heat, so that the division rate increases right up to the death point, with no sign of an optimum effect. Below 14° C. no observations are recorded.

Here, then, we have throughout the whole range exactly the same primary temperature relation exhibited by the protoplasmic procedure that we should expect for a chemical reaction in a test-tube.

This division phase is only a part of the life-cycle of the flagellate, and between division it swims about anabolizing the food material of the medium and growing to its full size ready for the next division. One wishes at once to know what is the effect of the temperature upon the length of the life-cycle. Is the whole rate of metabolism quickened in the same way as the particular section con-

¹⁸ Maltaux and Massart. *Recueil de l'Institut botanique Bruxelles*, Tome VI, 1906.

cerned with actual division? Of course a motile flagellate can not be followed and its life-cycle directly timed but the information was obtained by estimating carefully what percentage of individuals was in a state of actual division at each temperature. It was found that always 4 per cent. were dividing, whatever the temperature. This proves that the whole life-cycle is shortened in exactly the same proportion as the process of division at each temperature, and that it is just twenty-five times as long. Therefore the life-cycle is 125 mins. at 35° C. and 725 mins. at 15° C., so that here, again, we have the physical-chemical relation with a factor of 2.4 for each rise of 10° C.

In this paper of Maltaux and Massart these relations are not considered as the manifestations of physical-chemical principles, but are regarded as reactions to stimuli; and the paper contains a number of experiments upon the effect of sudden changes of temperature upon the occurrence of division. As far as one can make out from inspection of the scattered literature, it does seem established that sudden changes of temperature act as stimuli in the strict sense of the word. In many investigations one finds it stated that a quick change of temperature produced a certain reaction which a slow change of temperature failed to evoke. Usually all the phenomena are treated in terms of stimulation, and the absence of reaction with slow change of temperature is regarded as secondary. Were it not for the specific stimulatory effects of quick change, which are not difficult to comprehend as a phenomenon *sui generis*, I hardly think so general a tacit acquiescence would have been extended by botanists to the view that all enduring changes of velocity of metabolism brought about by lasting changes of temperature are stimulatory in nature.

No determination of the rate of development of bacteria through a very wide range of temperature seems to have been made. There are various incidental experiments which indicate values about 2 for the coefficient of increase of metabolism for a rise of 10° C.

I am not acquainted with any data for the growth rate of whole flowering plants at different temperatures: Of course the case of growth most usually measured in the laboratory, namely, where one part of a plant extends at the expense of the reserves stored in another part and there is a decrease, not an increase, of total dry weight, is not the type of growth we have to deal with. Even for simple elongation of a shoot at different temperatures we have but few data. Those of Koppen (1870) generally quoted are wildly irregular, and in many cases it is clear that the growth-extension of complex structures is a process which proceeds by spasms rather than smoothly.

The rate of movement of circulating protoplasm increases rapidly with temperature, but Velten's numbers do not give an obvious logarithmic curve. If we confine our attention to the values for 29° C. and 9° C. we do find, however, that the velocity increases about two-fold for each rise of 10° C. being 10 mm. at 9° C. and 40 mm. at 29° C.

Taken altogether these various data clearly support the hypothesis that temperature accelerates vital processes in the same way as it does non-vital chemical reactions, that is, logarithmically by an approximately constant factor for each rise of 10° C.; and, further, it accelerates them to the same extent; that is, that the factor in question has values clustering about 2-3.¹⁹

To make these similarities more significant I ought to point out that no other properties of matter are accelerated to anything like this extent by rise of temperature. Most reactions increase in velocity by no less than 10 per cent. per degree rise of temperature; a most marked effect, and yet there is no generally accepted explanation of this almost universal phenomenon. By the kinetic theory of gases each rise of a degree in temperature increases the movements of the gas-molecules, so that the

¹⁹ It has been proposed to use the size of the temperature coefficient to settle whether a process like the conduction of an impulse along a nerve is a chemical or a physical process. See Lucas, Keith. *Journal of Physiology*, Vol. XXXVII, June, 1908, p. 112.

number of collisions between them is greater, but only about $\frac{1}{6}$ per cent. greater. With rise in temperature, too, the viscosity of a solution diminishes, so that there is less resistance to internal changes; but this only to the extent of 2 per cent. per degree. The degree of ionization also increases, but only extremely little, so that no change of known physical properties will explain the phenomenon. Various hypotheses which need not detain us have been put forward.

Unexplained though it may be, yet the quantitative treatment of the subject is clear enough and, I think, as cogent in the living organism as in the test-tube. If so, we may consider ourselves now justified in separating off from the realm of stimulation yet a third class of causal connection, namely, that between temperature and general intensity of vital processes.

CONCLUSION.

In this attempt to assert the inevitableness of the action of physical-chemical principles in the cell, I have not ventured upon even the rudiments of mathematical form, which would be required for a more precise inquiry. Biochemistry is indeed becoming added to the ever-increasing number of branches of knowledge of which Lord Bacon wrote:

Many parts of nature can neither be invented with sufficient subtilty, nor demonstrated with sufficient perspicuity, nor accommodated unto use with sufficient dexterity, without the aid and intervening of the mathematics.

In this sketch which I have had the honor of outlining before you I have critically considered but few points. I have rather endeavored to distribute imperfect data in the perspective in which they appear from the point of view of one who seeks to simplify phenomena by extending the principles of chemical mechanics as far as possible into the domain of vital metabolism. Much critical quantitative work has yet to be done before the whole becomes an intelligible picture.

To me it seems impossible to avoid regarding the fun-

damental processes of anabolism, katabolism and growth as slow chemical reactions catalytically accelerated by protoplasm and inevitably accelerated by temperature. This soon follows if we once admit that the atoms and molecules concerned possess the same essential properties during their brief sojourn in the living nexus as they do before and after.

Perhaps the more real question is rather as to the importance and significance of this point of view. Protoplasmic activity might be something so much *per se*, and the other factors of the nature of stimuli might be superposed so thickly upon that substratum which should be dominated by simple principles of chemical mechanics that for practical purposes the operations of the latter would be so overlaid and masked as to be negligible. A survey of this field, however, seems to show that this is not so, and that the broad action of the law of mass and the acceleration of reaction-velocity by temperature are obviously responsible for wide ranges of phenomena.

Now the conception at the bottom of these principles is that of reaction-velocity, and the conclusion of the whole matter is that the physiologist must frankly take over from physical chemistry this fundamental conception.²⁰ Under definite conditions of supply of material and temperature there is a definite reaction-velocity for a given protoplasm, and the main factors that alter the rate of metabolism, viz., heat, nutrition and traces of impurities are exactly the factors which affect the velocity of reactions *in vitro*.

Working on this basis we no longer need the vague unquantitative terminology of stimulation for the most fundamental of the observed "responses" to external con-

²⁰ No general treatment of the physiology of plants has yet been attempted in terms of reaction-velocity. Czapek, however, in the introduction to his stupendous *Biochemie der Pflanzen*, Vol. I, 1905, does draw attention to the conception of "reaction-velocity" and refers to the standard literature on this subject and on catalysis, though direct application is not made to the plant. Cohen (*Physical Chemistry for Physicians and Biologists*, English edition, 1903) considers in detail some biological applications of the acceleration of reactions by temperature.

ditions. Three sets of phenomena we have observed which, though usually treated in the category of stimulation, draw a clearer interpretation from the conception of reaction-velocity. These were: (1) the relation of development to the absence or deficit of single essential food constituents; (2) the occasional striking effect of minute traces of added foreign substances upon the whole rate of growth and metabolism; and (3) the general doubling of the activity of vital processes by a rise of 10° C.

The next higher stratum of principles should be the complications introduced by limiting factors which interrupt the extent of the manifestations of these principles and by various correlations, as, for example, that by which the reaction-velocity of one catabolic process might withdraw the supply of material needed for full activity of another different process. To this sort of relation may be attributed that phenomenon so characteristic of the more complex vital processes and quite unknown in the inorganic world, namely, the optimum.

Finally, superposed upon all this comes the first category of phenomena that we are content still to regard as stimulatory. From the point of view of metabolism and reaction-velocity many of these appear very trivial, though their biological importance may be immense. Think how little the tropistic curvatures of stems and roots affect our quantitative survey; yet a little rearrangement of the distribution of growth on the two sides of an organ may make the difference between success and failure, between life and death.

From our present point of view vision does not extend to the misty conceptions of stimulation upon our horizon. We may therefore postpone speculation upon the mechanical principles governing them and await the time when by scientific operations we shall have reduced to law and order the intervening region, which we may entitle the chemical substratum of life. This done we may venture to pitch our laboratory a march nearer to the phenomena of protoplasmic irritability and make direct attack upon this dominating conception, the first formidable bulwark of vital territory.